UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/853,939	05/11/2001	Hiroshi Yanagawa	2001-0580A	7033

513 7590 11/04/2003

WENDEROTH, LIND & PONACK, L.L.P.
2033 K STREET N. W.
SUITE 800
WASHINGTON, DC 20006-1021

EXAMINER	
MITRA, RITA	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 11/04/2003

11

Please find below and/or attached an Office communication concerning this application or proceeding.

File Copy

Office Action Summary	Application No.	Applicant(s)	
	09/853,939	YANAGAWA ET AL.	
	Examiner	Art Unit	
	Rita Mitra	1653	

-- The MAILING DATE of this communicati n appears on the cover sheet with the correspondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *5,8-13 and 15-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,7 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5 and 8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

File Copy

DETAILED ACTION

Election/Restriction

Applicants' Response to Restriction Requirement, dated July 10, 2003 in paper #9, filed on August 11, 2003 (paper #10) is acknowledged. Applicant's election of Group I, claims 1-9 and 14 is acknowledged. Further Applicants have selected hormone receptor protein as a binding protein from claim 3 and a reporter protein green fluorescent protein from claims 4 and 5. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 10-13, 15-26 are withdrawn from further consideration by the Examiner as being drawn to a non-elected invention (37 C.F.R 1.142(b)). Claim 9, is withdrawn from further consideration as being drawn to a non-elected species. Claims 5 and 8 have been examined to the extent that they read on the elected species. Therefore, claims 1-8 and 14 are currently pending and under examination.

Objection to Claims

Claims 3-4 are objected to as to including non-elected species. However, to advance the prosecution, claims will be treated in the light of the Restriction Election. Therefore, only hormone receptor will be examined from claim 3 and green fluorescent protein will be examined from claim 4.

Claims 5 and 8 are objected to as to including non-elected species.

Claim 14 is objected to as for depending upon non-elected claim. It is incumbent upon applicant to properly amend the claims.

Priority

Applicant's claim for foreign priority under 35 U.S.C. 119 (a-d) is acknowledged. This application claims a priority of a Japanese Application No. 10/320102 filed November 11, 1998 Although, the instant application has provided a copy of this application, it fails to provide a certified copy of English translation in support of the priority date claimed. Therefore, the priority date November 10, 1999 would be considered for the priority date, which is a filing date of PCT/JP99/06261 application.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6 and 7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a sensor protein comprising an insert-type fusion protein composed of a reporter protein and a binding protein; does not reasonably provide enablement for all the sensor proteins composed of any binding proteins and any receptor proteins and fragments or mutants generated from any position located on the sequence of the sensor protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The invention includes a sensor protein comprising an insert-type fusion protein composed of a reporter protein and a binding protein, wherein said binding protein is inserted into the amino acid sequence of said reporter protein (claim 1), wherein the binding protein is a hormone receptor protein or a fragment or a mutant thereof (claim 3), wherein the reporter protein is a green fluorescent protein or a mutant thereof (claim 4, 6, 7). The specification,

however, only discloses cursory conclusions (see page 3, 8, 9, 18,), without data to support the findings. See the discussion below.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision In re Wands, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include: 1) the nature of the invention; 2) the breadth of the claims; 3) the predictability or unpredictability of the art; 4) the amount of direction or guidance presented; 5) the presence or absence of working examples; 6) the quantity of experimentation necessary; 7) the state of the prior art; and, 8) the relative skill of those skilled in the art;

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

The nature of the invention:

The nature of the invention is defined by the claims, which include a sensor protein comprising an insert-type fusion protein composed of a reporter protein and a binding protein, wherein said binding protein is inserted into the amino acid sequence of said reporter protein, wherein the binding protein is a hormone receptor protein or a fragment or a mutant thereof, wherein the reporter protein is a green fluorescent protein or a mutant thereof. However specification does not provide the information on the structure and function of the claimed fragments and mutants. The nature of the variation makes it entirely unpredictable what might be considered a variant before the isolation of such a sequence has actually taken place. For example, pages 3, 8, 9, 18 of the specification do not provide chemical, physical, and biological characteristics or function of fragments or mutants.

The breadth of the claims:

The breadth of the claims encompasses unspecified number of variants regarding the binding protein and the reporter protein components of sensor proteins, and fragments and mutants thereof, which are not specifically described or demonstrated in the specification.

Given the lack of teachings or guidance in applicants' disclosure regarding binding protein hormone receptor other than the one specifically referenced Ah receptor, it would require undue experimentation by one skill in the art to make mutants/fragments of Ah receptors or other undefined molecules having an activity substantially equivalent to that of Ah receptor, commensurate in scope with the claims. The specification indicates the general methods of generating mutants of the sensor proteins claimed at page 17-18. The specification fails to provide the positions in the sequence, which are critical to the protein's structure/function relationship, such as sites or regions directly involved in binding and activity.

The amount of direction or guidance presented;

The presence or absence of working examples; and

The quantity of experimentation necessary:

Given the breadth of the claims in the invention, detailed teachings are required to be present in the disclosure in order to enable the skilled artisan to make and use the mutants/fragments/variants of broadly claimed group of sensor proteins. Such teachings are absent in the specification. The specification has disclosed a sensor protein comprising a fusion protein composed of a binding protein (hormone receptor) and a reporter protein (green fluorescent protein), wherein the binding protein is inserted into the amino acid sequence of reporter protein. There is no guidance as to how the functional fragments and mutants of the claimed sensor protein or binding protein and/or reporter protein can be generated. The specification has provided no guidance to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein, which are tolerant to change (e.g. by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active protein variants, this is not adequate guidance as to the nature of active derivatives that may be constructed. The working examples are exclusively drawn to making one sensor protein, wherein the hybrid is composed of Ah receptor and GFP.

In consideration of each of factors, it is apparent that undue experimentation is necessary because in summary, the scope of the claim is broad, the working example does not demonstrate

the claimed variants, the guidance/the teaching in the specification is limited, and the outcome is unpredictable for the various modified forms. It is necessary to have additional guidance to carry out further experimentation to assess the property of the variants. Therefore, due to large quantity of experimentation necessary to generate the infinite number of variants and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required to in order to provide activity, the absence of working examples directed to same, the complex nature of the invention and the breadth of the claims, which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-4, 6 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 2 are indefinite as to the phrase "insert-type fusion protein." It is not clear as to the structure of the binding protein, which has been inserted to reporter protein, is it linear or branched?

Claims 3, 4 and 6-8 are indefinite as to the biological activity, size, sequence and physical characteristics of the mutants. Claim 3 is also rejected as to the use of "functional." It is not clear what is the activity of that fragment to be identified as "functional."

Claim 4 is also rejected as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim (See MPEP § 608.01(n)). Accordingly, the claim has been further treated on the merits as dependent solely from the first listed claim in

the claim dependency. Claim 4 is multiple dependent from a previous multiple dependent claim 3. It is incumbent upon applicant to properly amend the claims.

Claims 5 and 8 are indefinite as to the phrase "mutants thereof." It is not clear as to the number of mutations and number of added, substituted, and/or deleted amino acid residues at each mutation site. This mutant can be interpreted as a GFP.

Claim 14 is rejected as being dependent upon non-elected claims.

Claim Rejections – 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-4 and 6 are rejected under 35 USC 102 (a) as being anticipated by Baird et al. (Proc. Natl. Acad. Sci, USA, vol 96, pp. 11241-11246, Sep, 1999, IDS Ref No AQ, paper #5). Baird et al. teach a fusion protein wherein a receptor (calmodulin or Zinc finger protein, see col 2, page 11241 and col 1 and 2 at page 11242) is inserted into a green fluorescent protein (GFP). This fusion protein is considered for the sensor protein comprising an insert-type fusion protein composed of a reporter protein and a binding protein, wherein said binding protein is inserted into the amino acid sequence of said reporter protein of present invention (claim 1, 3). Baird's fusion protein's insert size is ~730 bp, which is expected to code an amino acid sequence of ~243 residues, therefore is considered for the binding protein having a size of 100 to 1000 amino acid residues in length of instant application, thus anticipating claim 2. Furthermore, Baird et al teach insertion of calmodulin or a Zinc finger domain in place of Tyr-145 of a yellow mutant (enhanced yellow fluorescent protein) of green fluorescent protein, wherein the GFP is modified by circular permutation which results in indicator proteins whose fluorescence

can be enhanced several fold upon metal binding (see abstract and col 1-2 at page 11241, and Fig. 6). Baird's indicator protein is considered for the sensor protein of current invention wherein the reporter protein is a mutant, thus anticipating claims 4 and 6.

Conclusion

No claims are allowable.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rita Mitra whose telephone number is (703) 605-1211. The Examiner can normally be reached from 10:00 a.m. to 6:30 p.m. on weekdays. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center number is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Rita Mitra, Ph.D.
November 1, 2003